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DB Name	Query	Hit Count	Set Name
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USPT	l1 same treat$	0	L2
USPT	c677T near0 muta$	1	L1

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L1: Entry 1 of 1 File: USPT Apr 17, 2001

DOCUMENT-IDENTIFIER: US 6218120 B1
TITLE: Methods for detecting human methylene tetrahydrofolate reductase allelic variants

DEPR:
A common mutation (C677T) results in a thermolabile enzyme with reduced specific activity (approximately 35% of control values in homozygous mutant individuals). Homozygous mutant individuals (approximately 10% of North Americans) are predisposed to mild hyperhomocysteinemia, when their folate status is low. This genetic-nutrient interactive effect is believed to increase the risk for neural tube defects (NTD) and vascular disease. There has been reported an increased risk for spina bifida in children with the homozygous mutant genotype for C677T. With the present invention, a second common variant in MTHFR (A1298C), an E to A substitution has been characterized. Homozygosity was observed in approximately 10% of Canadian individuals. This polymorphism was associated with decreased enzyme activity; homozygotes had approximately 60% of control activity in lymphocytes.

DEPR:
In addition, by virtue of the role of MTHFR in folate-dependent homocysteine metabolism, the C677T mutation predisposes to mild hyperhomocysteinemia, a risk factor for vascular disease, in the presence of low folate status. By the present invention, the frequency of the A1298C variant has been determined and its potential impact on enzyme function has been assessed.

DEPR:
Patients with spina bifida and mothers of patients were recruited from the Spina Bifida Clinic at the Montreal Children's Hospital following approval from the Institutional Review Board. Control children and mothers of controls were recruited from the same institution. Blood samples were used to prepare DNA from peripheral leukocytes, to assay MTHFR activity in lymphocyte extracts, and to measure total plasma homocysteine (tHcy). The presence of the C677T mutation (A to V) was evaluated by PCR and HinfI digestion (2). The A1298C mutation was initially examined by PCR and MboII digestion (5). The silent mutation, T1317C, was identified by SSCP and sequence analysis in a patient with severe MTHFR deficiency and homocystinuria. This patient, an African-American female, already carries a previously-described splice mutation (patient 354 (8)). Since this mutation also creates a MboII site and results in a digestion pattern identical to that of the A1298C mutation, distinct artificially-created restriction sites were used to distinguish between these 2 mutations. Detection of the A1298C polymorphism was performed with the use of the sense primer 5'-GGGAGGAGCTGACCAGTGCAG-3' and the antisense primer (5'-GGGGTCAGGCCAGGGGCAG-3'), such that the 138 bp PCR fragment was digested into 119 bp and 19 bp fragments by Fnu4HI in the presence of the C allele. An antisense primer (5'-GGTTCTCCCGAGAGGTAAAGATC-3'), which introduces a TaqI site, was similarly designed to identify the C allele of the T1317C polymorphism.

DEPR:
Since the C677T mutation (A to V) decreases MTHFR activity and increases homocysteine levels, the three genotype groups for the A1298C (E to A)

mutation were further stratified by the genotype for the A to V mutation, to avoid the confounding influence of the latter polymorphism on MTHFR activity and homocysteine levels. The frequencies of the 9 genotypes, with MTHFR activity and homocysteine levels for each genotype, are shown in Table 5. If the mothers and children without either mutation i.e. EE/AA are used as the reference (control) group, the mothers and children that are homozygous for the A1298C mutation (AAAA) have approximately 65% and 57%, respectively, of control MTHFR activity. Heterozygotes for the C677T change alone (EEAV) have approximately 70% of control activity, as reported in other studies, while double heterozygotes (EAAV), 18% of mothers and 11% of children, have an additional loss of activity (approximately 62% and 50% of control values, respectively).

DEPR:
Homocysteine levels were not significantly increased by the A1298C mutation, but homocysteine was levated (with borderline significance, p.ltoreq.0.07) in mothers and children who were homozygous for the C677T change. The small number of individuals who were homozygous for the A1298C mutation (n=13) may have influenced the power of the statistical analyses and precluded an investigation of the genetic-nutrient interactive effect that leads to mild hyperhomocysteinemia, as seen in individuals with the C677T mutation.

DEPR:
The A1298C mutation clearly reduces MTHFR activity, albeit to a lesser extent than the C677T mutation. Consequently its effect on homocysteine levels is also attenuated and, in fact, may only be significant when an individual carries both mutations and/or has poor nutrient status. However, since double heterozygotes are estimated to represent approximately 15% of the population, this variant should be examined in conjunction with the C677T ariant in studies of hyperhomocysteinemia.

DEPR:
The C677T mutation is a risk factor for hyperhomocysteinemia and has been implicated in both neural tube defects and vascular disease.

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End of Result Set

Generate Collection

L3: Entry 1 of 1 File: USPT Apr 17, 2001

DOCUMENT-IDENTIFIER: US 6218120 B1
TITLE: Methods for detecting human methylene tetrahydrofolate reductase allelic variants

DEPR:
Patients with spina bifida and mothers of patients were recruited from the Spina Bifida Clinic at the Montreal Children's Hospital following approval from the Institutional Review Board. Control children and mothers of controls were recruited from the same institution. Blood samples were used to prepare DNA from peripheral leukocytes, to assay MTHFR activity in lymphocyte extracts, and to measure total plasma homocysteine (tHcy). The presence of the C677T mutation (A to V) was evaluated by PCR and HinfI digestion (2). The A1298C mutation was initially examined by PCR and MboII digestion (5). The silent mutation, T1317C, was identified by SSCP and sequence analysis in a patient with severe MTHFR deficiency and homocystinuria. This patient, an African-American female, already carries a previously-described splice mutation (patient 354 (8)). Since this mutation also creates a MboII site and results in a digestion pattern identical to that of the A1298C mutation, distinct artificially-created restriction sites were used to distinguish between these 2 mutations. Detection of the A1298C polymorphism was performed with the use of the sense primer 5'-GGGAGGAGCTGACCAGTGCAG-3' and the antisense primer (5'-GGGGTCAGGCCAGGGGCAG-3'), such that the 138 bp PCR fragment was digested into 119 bp and 19 bp fragments by Fnu4HI in the presence of the C allele. An antisense primer (5'-GGTTCTCCCGAGAGGTAAAGATC-3'), which introduces a TaqI site, was similarly designed to identify the C allele of the T1317C polymorphism.

98022272 PubMed ID: 9380637
TI [Cerebral vascular complication of hyperhomocysteinemia. Controlling thromboembolic complications with folates].
Accident vasculaire cerebral avec hyperhomocysteinemie. Arret des accidents thromboemboliques sous folates.
AU Candito M; Bedoucha P; Jambou D; Appert-Flory A; Fisher F; Parrot-Roulaud F; Bayle J; Van Obberghen E; Chatel M
CS Laboratoire de Biochimie, Hopital Pasteur, Nice.
SO PRESSE MEDICALE, (1997 Sep 20) 26 (27) 1289-91.
Journal code: PMT; 8302490. ISSN: 0755-4982.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
LA French
FS Priority Journals
EM 199711
ED Entered STN: 19971224
Last Updated on STN: 20000303
Entered Medline: 19971110
AB BACKGROUND: Young **patients** who experience cardiovascular events may have raised levels of homocysteine. There may be several causes for this hyperhomocysteinemia. CASE REPORT: Cerebrovascular disease occurred in a 40-year-old female smoker with hyperhomocysteinemia. This **patient** subsequently had several episodes of thromboembolism involving the brain and lower limb arteries. Prothrombin concentration was
difficult to control with antivitamin K anticoagulants. Investigations to identify a **genetic** cause of hyperhomocysteinemia revealed that she was homozygous for the C677T **mutation** on the methylenetetrahydrofolate reductase **gene**. There was no G1691A **mutation** of the factor V **gene**, a risk factor for familial thrombosis. Supplementation with folic acid successfully halted episodes of thromboembolism (follow-up 2 years) and prothrombin levels stabilized under **treatment**. DISCUSSION: The C677T **mutation**, which is common in the **general** population (15.7%), cannot explain the effect of **folate** supplementation alone. Other **mutations** affecting homocysteine **metabolism** could have a potentialize effect on vascular events.

L11 ANSWER 7 OF 12 MEDLINE DUPLICATE 5
AN 95157813 MEDLINE
DN 95157813 PubMed ID: 7854589
TI Nutrition and alcohol neurotoxicity.
AU Manzo L; Locatelli C; Candura S M; Costa L G
CS Department of Internal Medicine, University of Pavia Medical School, Italy.
NC AA-08154 (NIAAA)
SO NEUROTOXICOLOGY, (1994 Fall) 15 (3) 555-65. Ref: 53
Journal code: OAP; 7905589. ISSN: 0161-813X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199503
ED Entered STN: 19950322
Last Updated on STN: 19980206
Entered Medline: 19950316
AB Neurological complications of alcoholism such as Wernicke-Korsakoff syndrome and polyneuropathy often originate from interactive factors

ANSWER 5 OF 12 MEDLINE DUPLICATE 3
AN 1998232425 MEDLINE
DN 98232425 PubMed ID: 9572710
TI Methotrexate in rheumatoid arthritis: an update with focus on mechanisms involved in toxicity.
AU van Ede A E; Laan R F; Blom H J; De Abreu R A; van de Putte L B
CS Department of Rheumatology, University of Nijmegen, The Netherlands.
SO SEMINARS IN ARTHRITIS AND RHEUMATISM, (1998 Apr) 27 (5) 277-92. Ref: 200
Journal code: UMV; 1306053. ISSN: 0049-0172.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199806
ED Entered STN: 19980611
Last Updated on STN: 19980611
Entered Medline: 19980604
AB OBJECTIVES: To provide an update of the current knowledge of the mechanism of action of low-dose methotrexate (MTX) in the **treatment** of **patients** with rheumatoid arthritis (RA), with an emphasis on the mechanisms involved in toxicity. We also considered strategies currently used to prevent or decrease toxicity of MTX. METHODS: We reviewed the literature dealing with the subjects of MTX **treatment** of RA, the mechanisms of action of low-dose MTX regarding efficacy and toxicity, and strategies used to prevent or decrease MTX toxicity. RESULTS: MTX is a fast working and effective second-line antirheumatic agent (SLA). Its use is limited mainly because of side effects. The mechanisms of action regarding efficacy and toxicity are probably determined by different **metabolic** pathways. Recent data indicate that the antiinflammatory effect of MTX is mediated by adenosine. However, MTX side effects can only partly be explained by **folate** antagonism and may also depend on its action on other related **metabolic** pathways. The latter include the homocysteine-methionine-polyamine pathway and purine **metabolism**. **Variants** in these **metabolic** routes (ie, the C677T **mutation** in the methylene-tetrahydrofolate reductase [MTHFR] **gene**), may predispose to the development of side effects. Currently the most promising strategy to decrease or prevent toxicity of MTX is concomitant prescription of folic acid or folinic acid. Other strategies are currently under investigation. CONCLUSIONS: MTX benefits a majority of RA **patients**. Approximately 30% of **patients**, however, abandon **treatment** because of drug-related side effects. Folic acid or folinic acid likely reduces MTX toxicity. More data, however, are needed to evaluate a potential detrimental effect on the antirheumatic efficacy of MTX.

ANSWER 4 OF 4 MEDLINE DUPLICATE 3

AN 96326384 MEDLINE

DN 96326384 PubMed ID: 8698850

TI Molecular basis of the human dihydropyrimidine dehydrogenase deficiency and 5-fluorouracil toxicity.

AU Wei X; McLeod H L; McMurrough J; Gonzalez F J; Fernandez-Salguero P

CS Laboratory of Molecular Carcinogenesis, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.

SO JOURNAL OF CLINICAL INVESTIGATION, (1996 Aug 1) 98 (3) 610-5. Journal code: HS7; 7802877. ISSN: 0021-9738.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 199609

ED Entered STN: 19960912
Last Updated on STN: 19960912
Entered Medline: 19960905

AB Dihydropyrimidine dehydrogenase (DPD) deficiency constitutes an inborn error in **pyrimidine metabolism** associated with thymine-uraciluria in pediatric **patients** and an increased risk of toxicity in cancer **patients** receiving 5-fluorouracil (5-FU) **treatment**. The molecular basis for DPD deficiency in a British family having a cancer **patient** that exhibited grade IV toxicity 10 d after 5-FU **treatment** was analyzed. A 165-bp deletion spanning a complete exon of the DPYD **gene** was found in some members of the pedigree having low DPD catalytic activity. Direct sequencing of lymphocyte DNA from these subjects revealed the presence of a G to A point **mutation** at the 5'-splicing site consensus sequence (GT to AT) that leads to skipping of the entire exon preceding the **mutation** during pre-RNA transcription and processing. A PCR-based diagnostic method was developed to determine that the **mutation** is found in Caucasian and Asian populations. This **mutation** was also detected in a Dutch **patient** with thymine-uraciluria and completely lacking DPD activity. A genotyping test for the G to A splicing point **mutation** could be useful in predicting cancer **patients** prone to toxicity upon administration of potentially toxic 5-FU and for **genetic** screening of heterozygous carriers and homozygous deficient subjects.

L12 ANSWER 2 OF 4 MEDLINE DUPLICATE 1
AN 1999141029 MEDLINE
DN 99141029 PubMed ID: 9988500
TI Antifungal drug resistance in pathogenic fungi.
AU Vanden Bossche H; Dromer F; Improvisi I; Lozano-Chiu M; Rex J H; Sanglard D
CS Janssen Research Foundation, Beerse, Belgium.. hvbossch@janbe.jnj.com
SO MEDICAL MYCOLOGY, (1998) 36 Suppl 1 119-28. Ref: 109
Journal code: C3Z; 9815835. ISSN: 1369-3786.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199904
ED Entered STN: 19990504
Last Updated on STN: 19990504
Entered Medline: 19990421
AB Failures of drug **treatment** in fungal infections combined with improvements in performances and standardization of antifungal susceptibility testing have drawn attention to the problem of antifungal resistance and its underlying mechanisms. Resistance of Candida species and Cryptococcus neoformans to flucytosine (5FC) develops during monotherapy. Acquired resistance results from a failure to **metabolize** 5FC to 5FUTP and 5FdUMP, or from the loss of feedback control of **pyrimidine** biosynthesis. A combination of 5FC and amphotericin B (AmB) reduces the appearance of resistant C. albicans isolates. Resistance to AmB is unusual. C. lusitaniae is the most susceptible to AmB resistance. C. neoformans with decreased AmB susceptibility has been isolated from an HIV-infected **patient**. Acquired resistance to AmB is often associated with alteration of membrane lipids, especially ergosterol. Concomitant with the widespread use of fluconazole there have been increasing reports of fluconazole resistance in Candida species and C. neoformans. Fluconazole resistance was mostly associated with prior use of fluconazole as intermittent therapy or prophylactic continuous **treatment** for recurrent thrush. In contrast to fluconazole, itraconazole is active against C. krusei. Decreased susceptibility to itraconazole is observed over time in C. albicans isolates becoming resistant to fluconazole. Decreased susceptibility to itraconazole and SCH-56592 was also observed in a few Aspergillus fumigatus isolates. Failure to accumulate azole antifungals has been identified as a cause of resistance in several post-**treatment** C. albicans, C. glabrata and C. krusei isolates. In azole-resistant C. albicans isolates from AIDS **patients** with oropharyngeal candidiasis, multidrug efflux **transporters** of the ATP-binding cassette (ABC) superfamily and of the class of major facilitators (MF) have been shown to be responsible for the low level of accumulation of azole antifungal agents. Two **genes** for these **transporters**, the ABC-**transporter gene** CDR1 and the MF **gene**, CaMDR1 (BEN) were shown to be overexpressed in resistant C. albicans isolates. Overexpression of BEN in Saccharomyces cerevisiae conferred resistance to fluconazole and terbinafine. CDR1 overexpression in S. cerevisiae conferred cross-resistance to fluconazole, itraconazole, ketoconazole and terbinafine. C. albicans clinical isolates resistant to azole antifungal agents over-expressing the ABC-**transporter genes** CDR1 and CDR2 were less susceptible to the morpholine derivative amorolfine. In C. glabrata isolates azole

resistance is based on over-expression of the CgCDR gene. A reduced susceptibility of ergosterol biosynthesis is another mechanism of resistance described in a number of post-**treatment** C. albicans, C. neoformans and Histoplasma capsulatum isolates. **Mutations** have been reported in the CYP51A1 **genes** of resistant C. albicans isolates. Over-expression of CYP51A1 in C. albicans and C. glabrata may also account for a decreased susceptibility to azole antifungal agents.

L12 ANSWER 3 OF 4 MEDLINE DUPLICATE 2
AN 97313755 MEDLINE
DN 97313755 PubMed ID: 9170156
TI Lack of correlation between phenotype and genotype for the polymorphically expressed dihydropyrimidine dehydrogenase in a family of Pakistani origin.
AU Fernandez-Salguero P M; Sapone A; Wei X; Holt J R; Jones S; Idle J R; Gonzalez F J
CS Laboratory of Metabolism, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.
SO PHARMACOGENETICS, (1997 Apr) 7 (2) 161-3.
Journal code: BRT; 9211735. ISSN: 0960-314X.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-U57655
EM 199707
ED Entered STN: 19970812
Last Updated on STN: 19970812
Entered Medline: 19970729
AB Dihydropyrimidine dehydrogenase (DPD) is the initial and rate-limiting enzyme in **pyrimidine** catabolism. DPD deficiency is associated with an increased risk of toxicity in cancer **patients** receiving 5-fluorouracil (5-PU) **treatment**. DPD deficiency causes an inborn error of **metabolism** called thymine-uraciluria that is in some instances associated with convulsive disorders and developmental delay in children. We have studied the molecular mechanism accounting for DPD deficiency in a Pakistani pedigree having 2-year-old child with thymine-uraciluria and exhibiting some degree of motor impairment and developmental delay. A common splice **mutation** was found in the **patient**'s dihydropyrimidine dehydrogenase (DPYD) **gene** that produces a **mutant** mRNA resulting in the complete lack of DPD protein and activity in lymphocytes and primary fibroblast. This trait segregated in the family following a typical Mendelian distribution. Surprisingly, the **patient**'s brother also had thymine-uraciluria and was homozygous for the splicing **mutation** but was clinically asymptomatic. Sequence tagged sites (STS) linkage analyses within 5 megabases of telomeric and centromeric DNA surrounding the DPYD **gene** revealed no allelic polymorphism between the two brothers. These results suggest that DPD deficiency might not be the only cause of the more severe clinical phenotypes observed in certain thymine-uraciluria **patients** and that an incomplete correlation between phenotype and genotype is present in the population.

L12 ANSWER 4 OF 4 MEDLINE DUPLICATE 3
AN 96326384 MEDLINE
DN 96326384 PubMed ID: 8698850
TI Molecular basis of the human dihydropyrimidine dehydrogenase deficiency and 5-fluorouracil toxicity.
AU Wei X; McLeod H L; McMurrough J; Gonzalez F J; Fernandez-Salguero P
CS Laboratory of Molecular Carcinogenesis, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.
SO JOURNAL OF CLINICAL INVESTIGATION, (1996 Aug 1) 98 (3) 610-5.
Journal code: HS7; 7802877. ISSN: 0021-9738.

CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199609
ED Entered STN: 19960912
Last Updated on STN: 19960912
Entered Medline: 19960905

AB Dihydropyrimidine dehydrogenase (DPD) deficiency constitutes an inborn error in **pyrimidine metabolism** associated with thymine-uraciluria in pediatric **patients** and an increased risk of toxicity in cancer **patients** receiving 5-fluorouracil (5-FU) **treatment**. The molecular basis for DPD deficiency in a British family having a cancer **patient** that exhibited grade IV toxicity 10 d after 5-FU **treatment** was analyzed. A 165-bp deletion spanning a complete exon of the DPYD **gene** was found in some members of the pedigree having low DPD catalytic activity. Direct sequencing of lymphocyte DNA from these subjects revealed the presence of a G to A point **mutation** at the 5'-splicing site consensus sequence (GT to AT) that leads to skipping of the entire exon preceding the **mutation** during pre-RNA transcription and processing. A PCR-based diagnostic method was developed to determine that the **mutation** is found in Caucasian and Asian populations. This **mutation** was also detected in a Dutch **patient** with thymine-uraciluria and completely lacking DPD activity. A genotyping test for the G to A splicing point **mutation** could be useful in predicting cancer **patients** prone to toxicity upon administration of potentially toxic 5-FU and for **genetic** screening of heterozygous carriers and homozygous deficient subjects.

(FILE 'HOME' ENTERED AT 08:41:15 ON 17 MAY 2001)

FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE, GENBANK' ENTERED AT 08:41:36 ON 17
MAY 2001

L1	8216	S	FOLATE (P) (TRANSPORT? OR METABOLI?)
L2	7698	S	PYRIMIDINE (P) (TRANSPORT? OR METABOLI?)
L3	1483	S	L1 (P)GENE?
L4	1073	S	L2 (P)GENE?
L5	557	S	L3 (P)(MUTA? OR VARIA?)
L6	331	S	L4 (P)(MUTA? OR VARIA?)
L7	81	S	L5 (P)TREAT?
L8	71	S	L6 (P)TREAT?
L9	22	S	L7 (P)PATIENT?
L10	11	S	L8 (P)PATIENT?
L11	12	DUPLICATE REMOVE	L9 (10 DUPLICATES REMOVED)
L12	4	DUPLICATE REMOVE	L10 (7 DUPLICATES REMOVED)